Scientists map water in molecular crystals, aiding drug development

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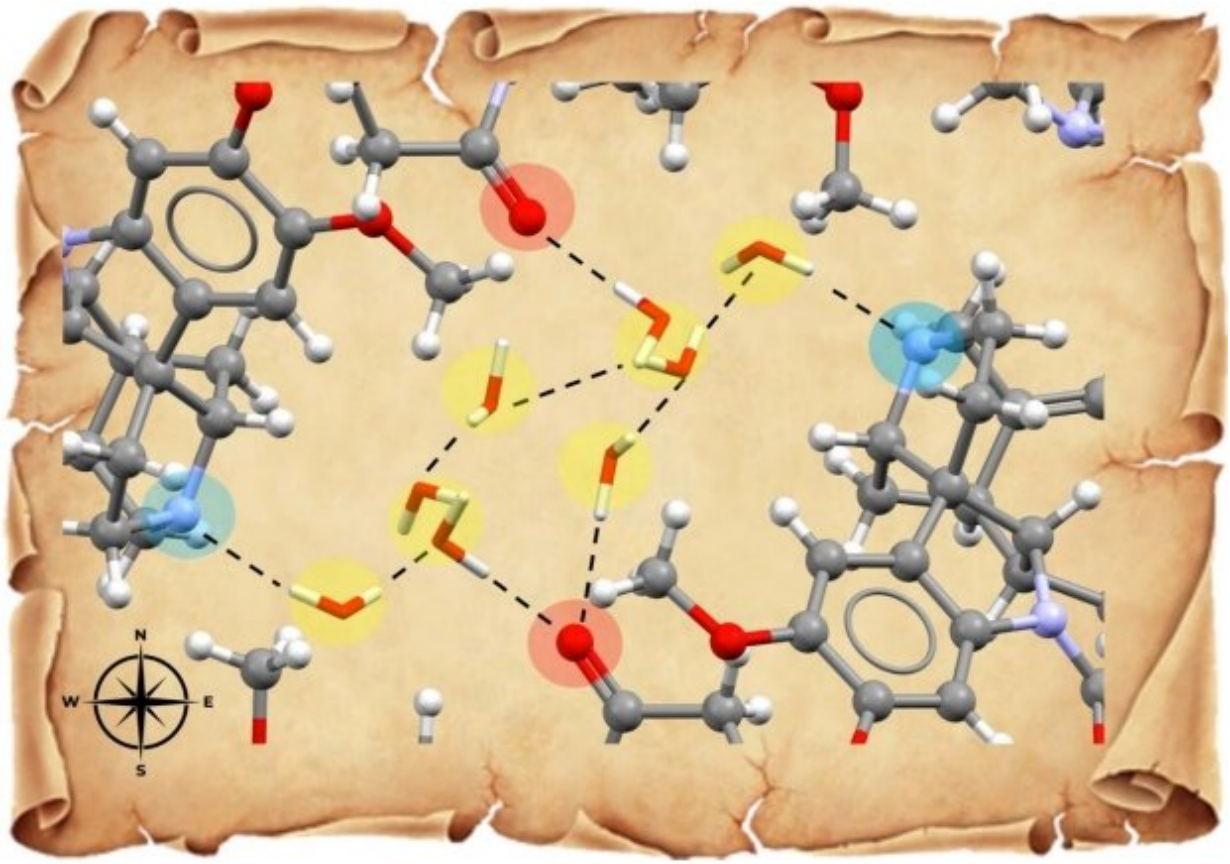

A new computational tool maps the position of water molecules in crystal structures. Credit: Richard S. Hong

Molecular crystals—the building blocks that make up many drugs and

other products—sometimes take on water molecules, which can alter the crystals in unforeseen ways. Notably, predicting which crystals are likely to contain water and at what level has been difficult and very computationally intensive. This problem is of significant industrial interest, especially in pharmaceuticals, yet the immense challenges associated with it require novel and efficient approaches.

Driven by these challenges, researchers at New York University, in collaboration with scientists at the biopharmaceutical company AbbVie, have developed a new computational tool that can quickly and efficiently map the position of water molecules within crystal structures. The findings, which appear in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), could be used during the drug development and discovery process to predict which crystals are likely to include water and anticipate the different possible structures of a given drug formulation.

Molecular crystals can take on water either during the crystallization process or by absorbing it from the environment. These water-holding crystals, known as crystal hydrates, represent a significant portion of patented drugs, and roughly one-third of commercially available drugs have active ingredients in hydrated form.

Adding water to crystals can change their properties—for instance, improving or impairing their ability to dissolve, which is critical for orally ingested drugs that must be absorbed to work. A crystal hydrate drug may also be considered a different formulation from a drug's dry form, raising the possibility of patent disputes.

This issue surfaced in the late 1990s and early 2000s in litigation over paroxetine hydrochloride (the antidepressant Paxil, a crystal hydrate), when a generic manufacturer tried to patent a dry version but was accused of patent infringement due to the dry form absorbing water

under humid conditions and converting to a hydrate.

"Industries that rely on crystal hydrates, from pharmaceuticals to agrochemicals to electronics, are faced with the challenge of predicting when hydrates will form and determining how the presence of water affects the properties of these crystals," said Mark Tuckerman, professor of chemistry and mathematics and chair of the Department of Chemistry at NYU, and the study's senior author.

To address this challenge, the researchers developed a computational protocol that can quickly determine whether a given compound will likely form a crystal hydrate. They devised a system for predicting both stoichiometric and non-stoichiometric hydrates, the latter of which has been notoriously hard to do.

Stoichiometric hydrates—which have a defined ratio of water molecules to other molecules—are not difficult to predict, but standard protocols require significant computational resources that can be time consuming and expensive. In contrast, there are no existing tools to easily and accurately predict non-stoichiometric hydrates, which do not have a defined ratio of water molecules to the other molecules in the crystal.

The researchers developed a protocol that they call MACH, or Mapping Approach for Crystal Hydrates. MACH establishes a set of rules to systematically determine where water would likely be inserted into a crystal based on the unique structure of and chemical environment within each crystal.

The MACH algorithm first instructs the computer to build a crystal structure in its dry form. It then tests to see if water will fit into the dry framework by overlaying a liquid water sample onto the crystal structure. Some water molecules will try to occupy the same space as the molecules of the host crystal, which violates basic laws of physics; these

water molecules are immediately eliminated by the MACH algorithm.

Next, MACH considers additional rules for how water will interact with the host crystal, further reducing the number and location of water molecules that can be incorporated into the crystal. These steps are then repeated many times with different configurations of water molecules.

"Because we know how water likes to interact with molecules in the host crystal, we can teach the computer to look for relevant patterns, such as hydrogen bonding," said Tuckerman. "Computationally, it's cheap and fast—we can do these steps thousands of times in a couple of hours."

At the end, the researchers are left with a map of the remaining water molecules, illustrating which crystals are likely to form hydrates—both stoichiometric and non-stoichiometric—and where the water molecules are incorporated.

The researchers demonstrated the ability of MACH to provide an accurate mapping of water molecules in three drugs: a plant-derived compound named brucine, the antidepressant paroxetine hydrochloride, and the diabetes drug sitagliptin tartrate.

The crystal structures of each drug have structural voids of different sizes and chemical environments—for instance, some are quite small, while others repel water—making them ideal tests for MACH to determine regions in which water can feasibly exist. Moreover, different crystal structures of these drugs (with and without water) were already confirmed in laboratory experiments, giving the researchers benchmarks to compare the water maps created using MACH.

"These computer-generated hydrate structures provide unique insights that can aid drug and materials design in identifying molecules that may be prone to hydrate formation," added Tuckerman. "Given its simplicity

and speed, MACH offers a promising tool for efficiently predicting hydrates and could be integrated into drug development and formulation workflows to build a more complete landscape of possible crystal structures."

"The development of MACH illustrates the synergies in university-industry collaborations for ready-to-implement conceptualization of novel approaches to solve pertinent industrial challenges," said Ahmad Sheikh, head of Solid State Chemistry at AbbVie and a study author.

More information: Richard S. Hong et al, A data-driven and topological mapping approach for the a priori prediction of stable molecular crystalline hydrates, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2204414119

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